HHS Public Access

Author manuscript

Trans R Soc Trop Med Hyg. Author manuscript; available in PMC 2016 March 18.

Published in final edited form as:

Trans R Soc Trop Med Hyg. 2015 October ; 109(10): 653–659. doi:10.1093/trstmh/trv074.

Implementation and evaluation of an isoniazid preventive therapy pilot program among HIV-infected patients in Vietnam, 2008–2010

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Abstract

Background—WHO recommends screening for TB and evaluation for isoniazid preventive therapy (IPT) based on evidence that they reduce TB-related morbidity and mortality among HIV-infected persons. In Vietnam, an IPT pilot was implemented in two provinces; TB screening, treatment and outcomes were evaluated to inform the adoption and scale-up of IPT.

Methods—During April 2008 to March 2010, eligible HIV-infected persons aged >15 years, with no previous or current TB treatment, alcohol abuse or liver disease were screened for TB. If TB disease was ruled out based on symptoms, chest x-rays and sputum smears, isoniazid was administered for 9 months.

Results—Among 1281 HIV-infected persons who received initial eligibility screening, 520 were referred to and evaluated at district TB clinics for TB disease or IPT eligibility. Active TB was diagnosed in 17 patients and all were started on treatment. Of 520 patients evaluated, 416 (80.0%)

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Authors' disclaimer: The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Competing interests: None declared.

Ethical approval: This project underwent formal ethical review by the U.S. CDC; it was determined to be a disease control activity, not human subjects research. As such, review by CDC institutional review board was not required.

Authors' contributions: TTT was involved in the design of the study, analysis and interpretation of the data, and drafting the manuscript; AHM and THL were involved in the conception and design and implementation of the study, acquisition and interpretation of the data, and critical revision of the manuscript; EB, DTH and SW were involved in the design of the paper, implementation of the study, interpretation of the data, drafting and critical revision of the manuscript; NVN and SND were involved in the implementation, interpretation of the data, draft and critical revision of the manuscript; TTV was involved in the implementation of the study, interpretation of the data, and critical revision of the manuscript; LTN was involved in critical revision of the manuscript, and administrative support. All authors read and approved the final manuscript. TTT is guarantor of the paper.

initiated IPT: 382 (91.8%) completed IPT, 17 (4.1%) stopped treatment, 8 (1.9%) died, 3 (0.7%) developed TB during IPT and 6 (1.4%) had unknown outcomes. No severe adverse events were reported.

Conclusions—IPT treatment completion was high; no serious complications occurred. Improving and expanding intensified case-finding and IPT should be considered in Vietnam.

Keywords

HIV/AIDS; Isoniazid; Preventive therapy; TB; Vietnam

Introduction

WHO has recommended that all HIV-infected persons be screened for active TB disease, and that HIV-infected persons without TB should be evaluated for treatment of latent TB infection, also known as TB-preventive therapy.[1] A course of isoniazid preventive therapy (IPT) for at least 6 months is recommended for all people living with HIV/AIDS (PLHIV) in whom active TB has been ruled out.[1] IPT has been shown to reduce the risk of active TB and death in PLHIV with few adverse events and without promoting drug-resistant disease.[2,3,4] Despite being safe, efficacious and recommended internationally, the uptake of IPT remains low at a global level. Based on the Global Plan to Stop TB, approximately 50% of patients newly enrolled in HIV care are expected to be eligible for IPT globally.[5] However, among 3.2 million eligible HIV-infected people worldwide, only 450 000 were provided with IPT in 2011, most of whom were from Africa.[6] Currently, only 21% of countries report any provision of IPT to people living with HIV.[7]

Vietnam has the 12th highest burden of TB in the world, with over 100 000 TB cases reported and an estimated annual incidence of 199 cases per 100 000 persons in 2011.[5] Among HIV-infected persons in Vietnam, TB has been found to be the primary cause of severe illness and death since 2006.[8] HIV prevalence among TB patients across Vietnam has risen from 5% in 2006 to 8% in 2011.[6,9] Furthermore, one study found that 20% of HIV-infected persons had radiographic evidence of prior or current TB disease when first screened.[10] During TB treatment, mortality rates in HIV-infected TB patients have averaged 20–30% compared to 3% in HIV-uninfected TB patients, with most deaths occurring during the first 3 months after TB diagnosis.[11] Program experience suggests that delayed diagnosis of HIV and TB and inadequate HIV treatment and care during TB treatment are contributing factors. Additional strategies to reduce the incidence of TB disease and transmission in Vietnam are needed. To improve HIV-associated TB control in Vietnam, an IPT pilot program was implemented in two provinces during 2008–2010. The objectives were to evaluate the screening, enrollment, treatment and treatment results and to document lessons learned to help inform Ministries of Health in Vietnam and other countries about the adoption and scale-up of IPT.

Materials and methods

HIV-infected persons receiving HIV care in either a home-based care program or outpatient clinics in selected districts in An Giang province and Hai Phong city were eligible for

inclusion in the pilot program. The long-standing home-based care program was established in Vietnam to facilitate treatment and care for TB and HIV patients through home visits by commune-level staff or by patient visits to commune health posts. HIV care is also provided in adult outpatient settings in hospitals and health centers.

An Giang province and Hai Phong city were selected as pilot sites because of their high burden of TB and HIV and the support of provincial and local leadership for piloting the IPTprogram within those areas. An Giang is a rural province located in the southern part of Vietnam near the Mekong Delta. Hai Phong is a port and industrialized city in the northern part of the country. During 2010,1695 PLHIV, 3126 TB patients and 214 HIV-infected TB patients were reported in An Giang. In Hai Phong, 6623 PLHIV, 2334 TB patients and 232 HIV-infected TB patients were reported.[12] The pilot program was implemented in 4 of 12 districts in An Giang and 2 of 14 districts in Hai Phong; these districts were selected based on the large number of patients registered in HIV care in these sites and the proven track record of a high level of commitment and engagement in TB/HIV activities by the district staff.

At the time of the pilot, WHO recommended IPT for PLHIV who were not currently receiving treatment for TB and had no symptoms suggestive of TB as defined by national TB guidelines.[13–15] Similarly, tuberculin skin tests were not recommended to determine eligibility in settings like Vietnam where the background rate of TB infection was estimated to exceed 30%.[15] Published studies indicated that symptoms, physical exam, chest radiography and sputum smears were sufficient to exclude most adult patients with pulmonary TB.[16,17] For the purposes of this pilot program, the most rigorous evaluation practically available was used to determine eligibility for IPT to ensure TB disease was ruled out and to minimize potential adverse events. Thus, for initial eligibility screening in this pilot, PLHIV already being managed in home-based care or in HIV outpatient clinics were pre-screened by trained TB and HIV staff at the commune level or HIV staff in out-patient clinics to exclude persons based on age (<15 years), alcohol abuse or chronic liver disease and current or previous TB treatment. Exclusions of patients from the second stage of IPTeligibility screening for other reasons (e.g., not currently living at home) were also recorded.

Eligible and willing persons were referred to the district TB unit (DTU) for further evaluation to confirm eligibility for IPT and to rule out TB disease. At the time this study was initiated, the best approach to screening for TB in PLHIV was not known. At DTUs, patients were evaluated by TB physicians using a checklist of TB history, signs and symptoms (i.e., cough for >2 weeks, hemoptysis, fever within the past week, extra-inguinal lymph node enlargement and rapid weight loss in the past month); laboratory evaluation included liver function enzymes, chest radiograph and three sputum smears for acid-fast bacilli (AFB). Patients were considered ineligible for IPT if they had any of the following: chest x-ray suggestive of TB disease; ≥1 AFB-positive sputum smear; any lymph nodes >1.5 cm; or liver function tests >3 times the normal range (aspartate aminotransferase [AST] 5–40 units/liter; alanine aminotransferase [ALT] 7–56 units/liter; bilirubin <21 Mmol). Eligible consenting persons who were willing to participate received their first month of 9

months' supply of 300 milligrams of isoniazid (INH) daily together with vitamin B6 from district TB staff.

Active TB was diagnosed if any of the sputum smear results were positive. For patients who had negative sputum smears, but signs or symptoms of TB or x-rays suggestive of TB disease, a group of TB physicians was convened to review the evidence before making a TB diagnosis as per national TB program guidelines. At the time of this evaluation, the Xpert MTB/RIF test was unavailable and access to TB culture was largely restricted to persons with suspected drug-resistant TB. If active TB disease was diagnosed, patients were treated following national TB program guidelines and were not eligible for IPT.

For those patients on IPT, subsequent administration of IPT was provided during monthly visits to commune health posts and outpatient HIV clinics, where patients were also monitored for TB symptoms and adverse drug reactions by TB and HIV staff (Figure 1). Patients who developed TB symptoms or adverse events, or who interrupted treatment for 2 months or more were referred by commune or HIV outpatient clinic staff to the DTU for more in-depth evaluation. TB staff followed patients during IPT treatment and recorded outcomes using standardized data collection forms at the DTUs.

Data were entered into a database (Microsoft Access 2009, Microsoft Corp., Redmont, CA, USA) and then imported to SAS version 9.2 (SAS Institute, Cary, NY, USA) for data analysis. Frequencies and proportions were calculated to describe the screening, enrollment, treatment and treatment outcomes for the pilot.

Results

During April 2008 to March 2010, a total of 1281 HIV-infected patients registered in home-based care and outpatient clinics were pre-screened for IPT eligibility: 623 (48.6%) were from An Giang and 658 (51.4%) from Hai Phong. Of these 1281 HIV-infected patients, 861 (67.2%) were male; mean age was 32 years (95% CI 32–33); 501 (39.1%) were unemployed and the median number of years since HIV diagnosis was 2 (range 0–14) (Table 1). Of the 431 (33.6%) patients found to be ineligible for the second stage of screening at the district level, 303 (70.3%) currently or previously had TB disease (Figure 2).

Of the 850 (66.4%) patients eligible for further screening at the district level, 520 (61.2%) presented to the district TB unit for further evaluation. Of these 520 patients, 302 (58.1%) were male; 131 (25.2%) were found to have symptoms consistent with TB, such as cough for >2 weeks (15.1%), cough with blood (0.9%), fever during the past week (10.1%), rapid weight loss during the past month (12.5%) or lymph node >1.5 cm (4.6%); 29 (5.5%) had an abnormal chest x-ray suggestive of TB (Table 2). Active TB was diagnosed in 17 (3.2%) patients. Including these 17 patients, 104 (20%) of the 520 patients who presented for further evaluation were ineligible for or unwilling to take IPT: 21 (4.0%) did not complete the screening evaluation; 10 (1.9%) patients evaluated at the district level were eligible, but declined IPT and 26 (5.0%) had elevated levels of liver enzymes (at least one value >3 times normal range) (Figure 2).

Overall, among the 416 patients who were initiated on IPT, the median years since HIV diagnosis was 2 (range 0–14); 199 (47.8%) patients were taking ART and 325 (78.1%) were taking cotrimoxazole (Table 3). Among the 320 patients with available CD4 counts, median CD4 count was 298 cells/mm^3 (range 1–1707); 179 (55.9%) patients had CD4 count <350 cells/mm^3.

During treatment, 19 (4.6%) of 416 patients overall were documented as having a symptom that might be consistent with TB, most commonly fever (4%), weight loss (2%) or cough (1%). Among the 416 patients, 92 (22.1%) reported having some type of side effect; the most frequently reported were fatigue in 55 patients(13.2%), loss of appetite in 42 patients (10.1%) and nausea in 25 patients (6.0%).

Of 416 HIV-infected patients who initiated IPT, 382 (91.8%) completed treatment. Thirty-four patients did not complete IPT: 17 (4.1%) stopped treatment, 8 (1.9%) died, 6 (1.4%) patients transferred to other clinics and 3 (0.7%) were diagnosed with active TB during IPT (Table 3). Of the eight patients who died while on IPT, all causes of death were related to late-stage AIDS (e.g., wasting, fungal infection), and were determined not to be TB- or IPT-related. Of the 17 patients who stopped treatment, three stopped because of side effects (one because of persistent itching, one because of vomiting and one because of elevated liver enzymes), seven stopped treatment because of loss to follow-up and one moved out of the district.

Discussion

Prior to 2008, IPT was not implemented as part of routine programmatic TB/HIV care and treatment services in Vietnam, even though it had been an internationally recommended strategy to reduce TB disease and mortality in PLHIV since 1998.[18,19] Based on our assessment of the uptake, screening, treatment and treatment completion rates during this IPT pilot program, scaling-up IPT was recommended for TB control among HIV-infected patients in Vietnam.

Overall, in this pilot program 32% (416/1281) of the PLHIV who initiated the screening process started on IPT. Screening for IPTeligibility among HIV-infected patients managed in home-based care and in outpatient HIV clinics was found to be a successful strategy. Approximately one-third of the patients pre-screened for IPT eligibility were excluded before referral to the district TB unit based on the eligibility criteria at the time; the vast majority of such patients were excluded because of previous or current TB disease.

Among patients who initiated IPT, completion of therapy was high: 92% of patients initiating IPT completed treatment, which is slightly higher but comparable to rates documented in other IPT pilot programs in Asia.[20] Staff received training prior to initiating the pilot and counseled patients before starting IPTabout adverse events and the disadvantages of stopping treatment, which may have helped reduce the drop-out rate in this pilot.

Adverse events attributable to IPT were few. Transient asymptomatic elevation in liver enzymes can occur after initiation of isoniazid,[21] and hepatotoxicity is a potential serious

adverse event during therapy.[22] However, with patient education about symptoms and close monitoring, the risks of hepatitis and death are very small, 0.10% and 0.001%, respectively.[22,23] In this pilot program, only one person had IPT stopped because of elevated liver enzymes and no TB- or IPT-related deaths occurred. Among the eight patients who died while on IPT of causes related to late-stage AIDS, only one patient was reported to be on ARTand three were on cotrimoxazole; CD4 count was available for only one patient. Taken together, these data suggest that the risks associated with IPT in this population are quite low.

In July 2012, the Ministry of Health of Vietnam adopted the current WHO guidelines supporting the use of IPT in HIV-infected patients,[1] including use of a validated TB symptom screening tool (current cough, fever, weight loss and night sweats), removal of a history of TB disease as a contraindication to IPT, improved TB diagnostic tests and oversight and delivery of IPT through the HIV program rather than the TB program. Some of the findings from our pilot program support the programmatic changes recommended in these guidelines.

The WHO policy statement on the use of IPT in PLHIV currently recommends a review of symptoms both to diagnose undetected active TB disease and to exclude from IPT patients who might have an increased risk of side effects.[1] Overall, one-quarter of patients in this pilot were reported to have symptoms consistent with TB during the second screening. The most commonly reported symptom was cough for more than 2 weeks. At the time of initiating this study, a validated symptom screening tool for TB diagnosis and determination of IPT eligibility did not exist. However, since then, a study of clinical algorithms for TB in PLHIV conducted in Cambodia, Thailand and Vietnam found that, while chronic cough alone was an insensitive predictor of TB, having ≥1 of several symptoms (i.e., night sweats ≥3 weeks, fever, cough) was found to be highly sensitive and simple to perform.[25,26] A large proportion of patients screened reported a history of TB disease, thereby excluding them from IPT based on the criteria for the pilot program. Growing evidence suggests that secondary preventive therapy (i.e., IPT for HIV-infected patients who have previously completed a course of TB treatment) is effective in reducing TB recurrence and does not increase risk of drug resistance.[1,3,27] Current WHO guidelines now recommend that HIV-infected patients previously treated for TB should be included for IPT.[1,23]

Diagnosing TB among PLHIV is notoriously difficult. In PLHIV, sputum smear is less sensitive than among HIV-negative patients, and a high proportion of HIV-infected TB patients can have negative results.[27–29] Sputum culture can diagnose TB in patients with negative sputum smears.[30] Among the 17 TB cases identified during screening, only one was smear-positive; 16 had a chest x-ray indicative of active TB. While chest radiography may aid in diagnosing patients with clinical symptoms who are smear negative,[27] there are limitations in interpreting films, particularly in PLHIV.[31,32] In addition, Xpert MTB/RIF may also be used to diagnose TB in HIV-infected patients following the current WHO guidelines on rapid implementation of the Xpert MTB/RIF diagnostic test.[33] According to these guidelines, all PLHIV with symptoms of TB should receive an Xpert MTB/RIF test as a primary TB diagnostic test. Then, if TB disease is not found, IPT should be offered.

In this pilot, the oversight and provision of IPT to PLHIV was through the national TB program in Vietnam. Unlike HIV staff, TB staff at the commune level are, in general, not as familiar with the HIV patients, have limited access to HIV medical history and clinic records, and are less experienced with the clinical management of HIV patients. As such, implementing the current WHO recommendations that IPT be managed and delivered through the HIV program can facilitate better care for PLHIV in Vietnam.[1,34]

Several limitations should be noted. The reasons for non-participation in the pilot program were not systematically collected so it was not possible to conclude why eligible persons opted out of initiating IPT. Additional research is needed to address this question. However, to better understand who was participating in the different steps of the screening process, demographic characteristics were compared for participants at the pre-screening stage, at the second screening at the district, and for those starting on IPT. While there was little difference in age and employment, the proportion of males participating at the different steps of the process decreased over time. It is possible that high completion rates among the patients started on IPT may have been due, in part, to bias introduced in the self-selection process among those showing up at the second screening. Also, by limiting the pilot program to only two sites that were selected based on their proven track record and high level of commitment to TB/HIV activities, success levels determined by the pilot may not be possible to generalize to the entire country. However, by including sites from the northern and the southern parts of the country and from rural and urban settings, we believe results and lessons learned from this project can provide useful insights into the roll-out of IPT in Vietnam, as well as other countries planning to implement IPT programs. Finally, the incidence of TB disease in HIV-infected patients who did and did not receive IPT were not compared because evaluating the effectiveness of IPT was outside the scope of this work, since the effectiveness of IPT is already well-documented.[2–4] Instead this project aimed to describe the more practical aspects around IPT implementation and lessons learned to inform future scale-up in Vietnam and other countries. A strength of the project is that it demonstrated that screening PLHV for TB and treating them with IPT is successful in Vietnam, as evidenced by the: 1. high rate of PLHIV who initiated IPT; 2. high retention rates while on IPT (92%); and 3. minimal adverse events.

The new IPT program in Vietnam is situated within the HIV program, per international guidelines, and many of the lessons learned from this pilot program have since been applied. In HIV outpatient clinics, intensified case finding for TB, based on the use of the validated symptom screening tool, is now a component of routine HIV care, as recommended by WHO and national guidelines.[1,31] Furthermore, HIV-infected patients with a history of previous treatment for TB are now offered IPT, thereby increasing the numbers of patients who may benefit from such therapy. These integrated efforts for improving TB case finding among HIV-infected patients and identifying HIV-infected patients who are eligible for IPT are critical for reducing TB morbidity and mortality among HIV-infected people in Vietnam.

Acknowledgments

Funding: This project has been supported by the President’s Emergency Plan for AIDS Relief (PEPFAR) through the U.S. Centers for Disease Control and Prevention (CDC) under the terms of Cooperative Agreement project number [1U2GPS000747].

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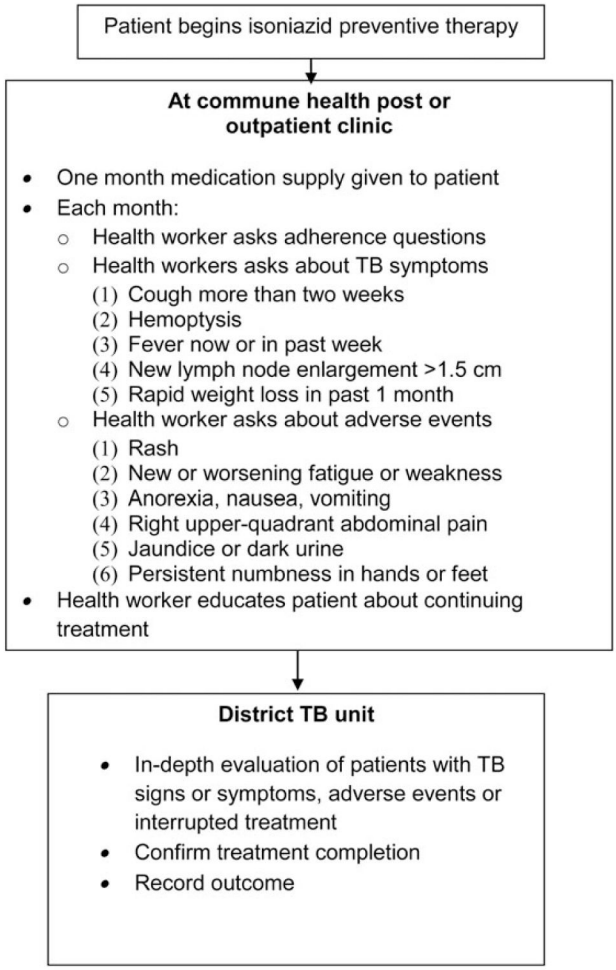

Figure 1.
Algorithm for monitoring during treatment in this study.

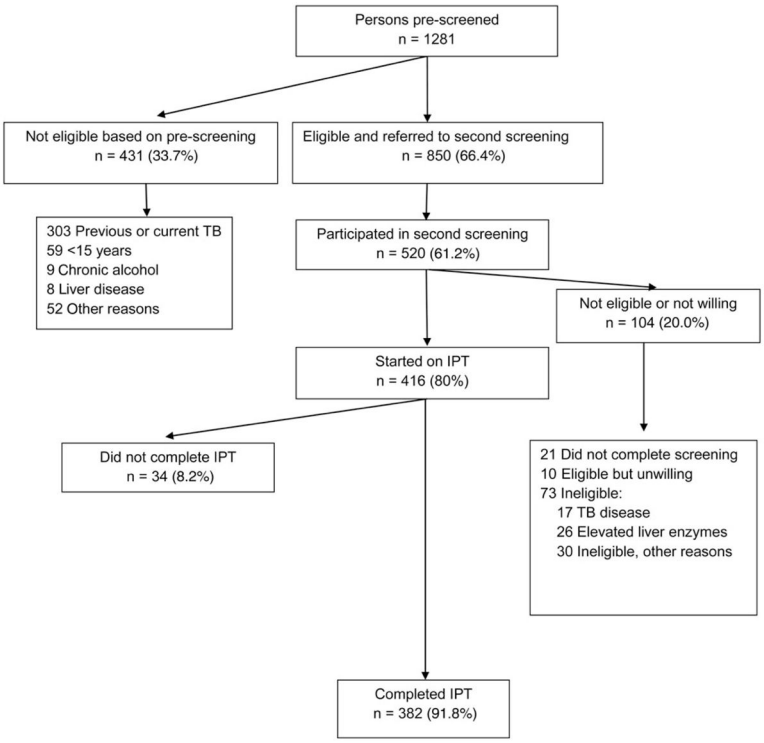

Figure 2.
Isoniazid preventive therapy (IPT) pilot program results.

Table 1

Characteristics of persons with HIV infection enrolled in home-based care or outpatient clinics who were pre-screened (n=1281)

Characteristics	Total, n=1281 n (%)
Male	861 (67.2)
Age in years	
≤15	59 (4.6)
16–30	434 (33.9)
31–45	696 (54.3)
46–60	85 (6.6)
>60	7 (0.5)
Occupation	
Unemployed	501 (39.1)
Student or children	55 (4.3)
Agriculture or fishing	95 (7.4)
Labor	187 (14.6)
Business or government	103 (8.0)
Other occupation	332 (25.9)
Missing	8 (0.6)
Years since HIV diagnosis	
<3	694 (54.2)
>3	563 (44.0)
Missing	24 (1.9)

Table 2

Results of isoniazid preventive therapy (IPT) eligibility screening at district TB unit (n=520).

Characteristics	Total n=520 n (%)
Symptom screening[a]	
Any of the symptoms below	131 (25.1)
Cough for more than 2 weeks	79 (15.1)
Cough up blood in past 2 weeks	5 (0.9)
Fever now or in past week	53 (10.1)
Rapid weight loss in past one month	65 (12.5)
Lymph node >1.5 cm on exam	24 (4.6)
Liver function tests	
High liver enzyme test result[b]	26 (5)
Liver enzyme test result within range	445 (85.6)
No liver test done	49 (9.4)
Sputum smear	
Positive sputum smear	1 (0)
Negative sputum smear	411 (79.0)
Not done or missing or no cough	108 (20.8)
Chest x-ray	
Abnormal chest x-ray, suggestive of TB	29 (5.6)
Abnormal chest x-ray, not-TB	49 (9.4)
Normal chest x-ray	430 (82.7)
Not done	12 (2.3)

[a] More than one option applies. Totals do not equal 100%.

[b] At least one value >3 times normal range: normal ranges are: aspartate aminotransferase 5–40 units/liter; alanine aminotransferase 7–56 units/liter; bilirubin <21 Mmol.

Table 3

Characteristics and isoniazid preventive therapy (IPT) outcome among patients started on IPT (n=416).

Characteristics	Total n=416
Male, n (%)	210 (50.4)
Unemployed, n (%)	147 (35.3)
HIV information	
Years since HIV diagnosis, median (range)	2 (0–14)
CD4[a] count at start of IPT, median (range)	298 (1–1707)
0–200, n (%)	112 (26.9)
201–350, n (%)	67 (16.1)
>350, n (%)	141 (33.8)
Missing, n (%)	96 (23.0)
TLC median (range)	2300 (600–8300)
Taking ART, n (%)	199 (47.8)
Years on ART prior to IPT median (range)	0.8 (0.0–4.2)
Taking cotrimoxazole, n (%)	325 (78.1)
Years on cotrimoxazole prior to IPT, median (range)	1.43 (0.0–8.6)
Taking fluconazole, n (%)	10 (2.4)
Treatment results	
Completed treatment, n (%)	382 (91.8)
Died during treatment, n (%)	8 (1.9)
Stopped treatment, n (%)	17 (4.1)
Developed TB during IPT, n (%)	3 (0.7)
Transferred to another clinic, n (%)	6 (1.4)

ART: antiretroviral therapy; IPT: isoniazid preventive therapy; TLC: total lymphocyte count.

[a]CD4 count: a measure of the number of helper T cells per cubic millimeter of blood, used to analyze the prognosis of patients infected with HIV.